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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/203,004	BERD, DAVID	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *43,44,47,49-62,64-72 and 74-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *43-44, 47, 49-62, 64-72, 74-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Appeal Brief submitted January 5, 2007, in response to the Office Action of December 5, 2006 is acknowledged and has been entered. However, upon review and reconsideration the finality of the previous office action is hereby withdrawn. Claims 43-44, 47, 49-62, 64-72, 74-77 are currently being examined.

2. Examiner has established a priority date of February 28, 1994 for claims 47, 65-72, 74-77 because the claims are drawn to a method of treating wherein the therapeutic composition is administered at least six times at spaced apart intervals. However, a review of parent application 07/985,334, now US Patent No. 5,290,551 does not reveal any support for the claimed limitation. Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The following rejections are being maintained:

Claim Rejections - 35 USC § 103

5. Claims 43, 44, 49-62, 64 remain rejected for the reasons previously set forth in the paper mailed November 29, 2000, Section 7, pages 5-6.

Applicant argues at page 20 of the Appeal Brief that the Braun Declaration addresses the teachings and deficiencies of the primary reference, Berd 1989 and states that the Berd 1989 reference lacks teachings with respect to any clinically significant tumor regression being observed as well as numbers and route of administration of the cancer cells. Applicant points to the Braun Declaration paragraphs 9 and 11. Applicant concludes that one of ordinary skill in the art would have presumed that Berd 1989's haptenized tumor cells and BCG had been

injected intra-tumorally and that the BCG was thereby responsible for the observed, clinically non-significant tumor responses.

A review of paragraph 9 of the declaration reveals that paragraph 9 is not drawn to clinically significant tumor regression, although it is drawn to a discussion of a definitive protocol which appears to be what Applicant is referring to when arguing "numbers and route of administration of cancer cells.

Dr. Braun argues that the abstract is deficient because it does not provide a definitive protocol for administration of the cells, doesn't teach how to conjugate the DNP or describe an effective protocol and in the absence of these details one of ordinary skill would be unable to practice the technology predictably. The argument has been considered but has not been found persuasive because the abstract does indeed teach a definitive protocol wherein patients with metastatic melanoma were sensitized to DNP by topical application of DNCB. Two weeks later they were injected with a vaccine consisting of 10-25 x 10(6) autologous, irradiated melanoma cells conjugated to DNP and mixed with BCG. CY 300 mg/M2 IV was given 3 days before DNCB or vaccine. Further, the abstract specifically states that "treatment of melanoma patients with autologous vaccine" that is autologous melanoma cells that are not haptenized "preceded by low dose cyclophosphamide induces delay-type hypersensitivity to melanoma cells and in some cases, regression of metastatic tumors", clearly indicating that the definitive protocol was known in the art. Given this statement, the skilled artisan would have looked to the art, in particular Berd et al (Cancer Research, 1986, Induction of Cell-Mediated Immunity to Autologous Melanoma Cells and Regression of Metastases after Treatment with a Melanoma Cell Vaccine Preceded by Cyclophosphamide, 46:2572-2577) for guidance drawn to the definitive and

effective protocol. The argument has been considered but has not been found persuasive because contrary to Dr. Braun's argument, given the teachings of the abstract and that which was known in the art, one of ordinary skill could practice the claimed invention with a reasonable expectation of success.

At paragraph 11, Dr. Braun argues that there is no indication that the patients described in the Berd 1989 abstract received any clinical benefit. In particular, the descriptions of inflammatory reactions, CD4 and CD8 infiltration and fluid accumulation is no indication of clinically significant tumor regression which is defined by those practiced in the art as greater than 50% reduction in tumor size without concomitant progression at other sites. Further, given the teachings of Fujiwara of the effects of sensitization with DNCB and DNP-modified tumor cells, the inflammatory reactions, CD4 and CD8 infiltration and fluid accumulation would have been expected because the patients had been sensitized to DNCB and then injected with DNP-modified tumor cells. The argument has been considered but has not been found persuasive although Dr. Braun admits on the record the known sensitization effects of DNCB and DNP-modified tumor cells, Dr. Braun is arguing limitations not recited in the claims as currently constituted as neither the specification nor the claims as originally filed is drawn to or requires "significant treatment" nor that there be 50% reduction in tumor size without concomitant progression at other sites. The claims are specifically drawn to a composition and a method for treating a malignant tumor wherein a set of defined responses to the treatment are claimed. Given that the abstract clearly teaches that tumors were beginning to regress the abstract clearly teaches that the tumors were treated.

Applicant argues that Wiseman teaches a successful alternative form of immunotherapy that depends upon intralymphatic immunization and Wiseman in

no way suggests a deficiency or problem that would lead one of ordinary skill in the art to seek an alternative immunization strategy. The argument has been considered but has been found persuasive because Berd et al specifically teach, and in fact demonstrate, the increased efficiency of cancer cell vaccine with haptenization and sensitization. Thus, although Wiseman in no ways suggests a deficiency or problem that would lead one of ordinary skill in the art to seek an alternative immunization strategy, as previously set forth, it would have been *prima facie* obvious to modify the cells of Wiseman et al to increase the efficiency of the already successful treatment procedures.

Applicant argues that the Geczy reference teaches away from the claimed invention and any notion that the haptenized tumor cells could yield an anti-tumor response because they suggest an anti-hapten response and do not relate to cancer treatment, do not teach DNP haptenized tumor cells wherein the patient is sensitized with 1-fluoro-2,4-nitrobenzene prior to administration of cyclophosphamide. The argument has been considered but has not been found persuasive because the Geczy reference was cited only to provide a nexus between and demonstration of the functional identity of the DNCB successfully used by Berd et al, 1989 abstract and the claimed DNFB.

Applicant argues that even if Berd, 1989 had taught an effective immunotherapy of melanoma using haptenized, autologous melanoma cells, such a teaching would not form a sufficient basis for combination with Wiseman to achieve the claimed invention because Hoover et al, of record specifically demonstrate that although colon cancer cells are effective as a vaccine (see Hanna, of record), rectal cancer cells are not, thus, it cannot be predicted which tumor cells would be effective in haptenized vaccines for the treatment of cancer.

The argument has been considered but has not been found persuasive because although Berd et al, 1989 and the instant specification teach that autologous, irradiated melanoma cells and Hanna teaches that autologous irradiated colon cancer cells are effective for treating the respective cancers in the absence of haptenization, Hoover makes clear that there is not a similar finding for rectal cancer cells. Thus, unlike cells which have been shown to effective vaccines, the rectal cancer cells are in fact not effective vaccines, due perhaps to a difference in the immunogenicity of the cells, or other reasons. Given that Wiseman teaches a wide variety of cancer cells that are effective for anticancer treatment, given that the method of Berd et al would simply be expected to increase the efficiency of the vaccine as disclosed in the abstract it would be expected and thus could be predicted that when haptenized, cancer cells already demonstrated to be successful for treating cancer would continue to be effective for treating cancer and the claims are obvious for the reasons of record.

The argument has been considered but has not been found persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 43-44, 47, 49-62, 64-72, 74-77 are rejected under 35 USC 112, first paragraph because the specification, while being enabling for a composition and a method of treating a malignant tumor in a human patient wherein the malignant tumor is melanoma, colon cancer, lung cancer or kidney cancer comprising administering autologous haptenized melanoma cells, colon cancer cells, lung cancer cells or kidney cancer cells admixed with adjuvant, wherein the cells have been rendered incapable of growing in a body of a human upon injection therein, does not reasonably provide enablement for a method for treating a malignant tumor in a human patient comprising administering autologous haptenized tumor cells admixed with adjuvant, which when administered together with an adjuvant, wherein the cells have been rendered incapable of growing in a body of a human upon injection therein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to practice the invention commensurate in scope with these claims.

The claims are drawn to a method for treating a malignant tumor in a human patient comprising administering autologous haptenized tumor cells admixed with adjuvant, which when administered together with an adjuvant, wherein the cells have been rendered incapable of growing in a body of a human upon injection therein. This means treatment with any type of tumor cell.

The specification teaches that the present invention is directed for use in treating cancer, including metastatic and primary cancers. Cancers treatable with the present invention include the following non-limiting examples: melanoma,

breast, lung, colon, breast, kidney, and prostate (p. 11, lines 19-25). The specification exemplifies the successful treatment of patients with metastatic melanoma with the claimed invention (see Examples 1-7).

One cannot extrapolate the teaching of the specification to the scope of the claims because the only mention or guidance drawn to any cancer type other than melanoma in the specification as originally filed is the single sentence found at page 11, lines 19-25. In particular, Applicant effectively argued in the Response submitted November 11, 1999 (and reiterated in the instant Appeal Brief) that "Berd does not teach or provide any reasonable expectation of success in achieving treatment for any tumor, and particularly for treating lung cancer, colon cancer, breast cancer, kidney cancer, and prostate cancer. The other references cited by the Examiner do not supply the missing teaching....." (para bridging pages 7-8) and again at page 13 of the Response, Applicant states that "As discussed above, there is no reasonable expectation of successfully implementing the vaccination program described with respect to melanoma in Berd to other tumor types. This reference provides "preliminary" results that "may represent a significant advance in the immunotherapy of human melanoma." Thus, it lacks any reasonable expectation of an effective treatment for tumors in general." Examiner agrees with Applicant that Berd et al, alone does not provide a reasonable expectation of success for treatment of any tumor. Given that the specification, like Berd et al, provides no information drawn to treatment of any tumor other than melanoma, except the single statement at page 11 of the specification, it would also appear that the instantly claimed treatment drawn to any tumor type is also not enabled. However, the literature, in combination with Berd et al, 1989 provides the missing information and for the reasons of record, the claimed invention, drawn to treatment of melanoma, colon

cancer, lung cancer or kidney cancer is not only enabled but obvious over the prior art (see the paper mailed April 28, 1999, Section 12, pages 15-18) and thus an enablement rejection was not previously applied.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Some of Applicants arguments in the Appeal Brief at pages 22-23 are relevant to the instant rejection.

Applicant basically reiterates the arguments of November 1, 199 and specifically argues that

"Even if Berd 1989 had taught an effective immunotherapy of melanoma using haptenized, autologous melanoma cells, such a teaching would not form a sufficient basis for combination with Wiseman to achieve the claimed invention. As applicants have previously pointed out, it is not expected that "vaccines using other types of tumor cells, shown to effectively treat cancer, would behave in a mechanistically similar manner to the melanoma vaccine described in Berd et al."

Applicant points to Hanna et al. US Patent No. 5,484,596, submitted December 1, 1998 and argues that although Hanna teaches a method for the treatment of human colon cancer that involves the use of a vaccine which is made from irradiated human tumor cells, the strategy of Hanna appears to be effective only for treating colon cancer, apparently supporting the argument that the combined prior art does not provide a reasonable expectation of success for any

tumor. Applicant further points to Hoover et al. (J. Clin. Oncology 11: 390-399, 1993), of record, wherein Hoover states that "... no benefits were seen in patients with rectal cancer who received [active specific immunotherapy with an autologous tumor cell-BCG vaccine]". Applicant goes on to argue that "even though the Hanna vaccine was reportedly successful in treating colon cancer, it failed to provide any benefits to patients with rectal cancer, a tumor type closely related to colon cancer. Accordingly, even had Berd 1989 successfully treated melanoma patients with his haptenized tumor cell vaccine, and not only provided preliminary and essentially anecdotal results relating to DTH-responses, it could not have been reasonably expected that a similar vaccine would be equally effective in the treatment of related tumors, much less tumors of completely unrelated origin."

The argument has been carefully considered but was not found persuasive because a careful review of Hoover et al reveals that the reference reports on a previous clinical trial wherein successful treatment of colon cancer patients with autologous, irradiated colon cancer cells admixed with BCG was demonstrated, wherein the treated patients had both increased survival and disease free survival compared to untreated controls (see p. 391). Further, the reference describes the results of a Phase III trial wherein not only colon cancer patients were treated with the autologous tumor cell vaccine but also rectal cancer patients were treated with autologous tumor cell vaccine (see abstract). As Applicant has stated, while the colon cancer patients benefited from the treatment, the rectal cancer patients did not. The authors specifically state "That colon cancer patients appear to benefit while rectal cancer patients do not is of considerable interest." The authors then hypothesize that "It could be that rectal cancers are intrinsically less immunogenic"

or that the lack of effect in the rectal cancer patients could be related to treatment protocols of the rectal cancer patients (p. 397, column 1). However, it is clear that it was unknown why the rectal cancer patients did not benefit from the treatment. It is noted that a search of the literature did not reveal, unlike the colon cancer, kidney cancer, lung cancer studies of the Wiseman et al, the colon cancer studies of Hanna and melanoma studies disclosed in Berd et al, 1989, any instance of successful treatment of rectal cancer with autologous, irradiated tumor cells. Although it would be expected that hapentization (a known stimulator of the immune system as clearly admitted on the record as set forth above) would result in increased efficiency of a vaccine with demonstrated efficacy, it could not be predicted and in fact would not be expected that stimulation of the immune system by hapenization alone, in the absence of the ability of autologous tumor cells to effectively treat a tumor, for example due to intrinsically poor immunogenicity, would in fact result in an effective treatment. This finding is supported both by the Hoover reference and Applicant's arguments in the Appeal Brief. The Hoover reference at page 397, column 1 specifically teaches that although both colon cancer patients and rectal cancer patients treated with a combination of autologous tumor cells and BCG (also a known stimulator of the immune system as admitted on the record by Applicant, see Appeal Brief at page 20) tested positive for DCH with autologous tumor cells (p. 396, col 1), only the colon cancer patients were effectively treated. Thus, it is clear that although both treatment protocols stimulated the immune system and the rectal cancer patients mounted an immune response, apparently in response to the BCG component of the vaccine, the immune response was not sufficient for treatment. Thus stimulation of the immune system, in the absence of demonstrated effectiveness of the autologous tumor cell

vaccine in the absence of haptenization, is clearly not enough to predictably result in effective cancer treatment. It appears that Applicant is indeed correct, that the information in the Hoover references raises the question of a reasonable expectation of success and the enablement of the broadly claimed invention, wherein it cannot be predicted, in the absence of objective evidence that a cell type is useful for effectively treating a tumor in the absence of haptenization, that the invention will function as claimed.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

8. Claims 47, 65-72, 74-75, 77 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "repeating said administration at least six times at spaced apart intervals" set forth in claim 47, newly added on August 6, 1997, has no clear support in the specification and the claims as originally filed. In the paper filed August 6, 1997, page 6, Applicant points to support for the newly added limitation at Examples 5 and 6 and at page 29 lines 2-3 of the specification. However, a review of the cited support reveals that Example 5 provides support only for "DNP-vaccine was repeated every 28 days" and support for collection of PBL after 2 vaccines, after 4 vaccines and after 8 vaccines. Further, a review of Example 6 reveals support only for DNP-conjugated vaccine "was injected every 28 days for a total of 8 treatments". Further, a review of page 29, lines 2-3 reveals that lines 2-3

provide support only for "Patients were treated with eight courses of vaccine which required about eight months". The support has been considered but has not been found persuasive because nothing in the cited support is drawn to the new broadly claimed regimen of administration. The subject matter claimed in claims 47, 65-72, 74-75, 77 broadens the scope of the invention as originally disclosed in the specification.

9. Claims 47, 65-72, 74-75, 77 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "wherein said composition elicits at least one of the following upon administration.....an inflammatory immune response.....a delay-type hypersensitivity response.....activated T lymphocytes that infiltrate the tumor" set forth in claim 47, newly added on August 6, 1997, has no clear support in the specification and the claims as originally filed. In the paper filed August 6, 1997, page 6, Applicant points to support for the newly added limitation at a various pages and specifically states support for each of the elicited responses separately. However, a review of the cited support reveals only a single page where two of the elicited responses are found together. A specific review of page 18, lines 8-9 reveals that the citation supports only "Patients were evaluated to determine whether tumor regression had occurred, to monitor tumor inflammatory responses, and to measure delayed type hypersensitivity to autologous melanoma cells". The support has been considered but has not been found persuasive because nothing in the cited support is drawn to elicitation of "at least one" of the elicited reactions as now broadly claimed. The subject matter claimed in claims 47, 65-72, 74-75, 77 broadens the scope of the invention as originally disclosed in the specification.

10. Claims 76-77 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of ""predominantly CD8+CD4" set forth in claims 76 and 77, newly added on December 3, 1998 and November 1, 1999, has no clear support in the specification and the claims as originally filed. In the response submitted December 3, 1998, Applicant states that page 23, lines 5-7 support the newly added limitation. A review of the specification at page 23, lines 5-7 reveals support for "Biopsies showed infiltration with lymphocytes ..... were mainly CD3+, CD4-, CD8+, HLA-DR+ T cells. The suggested support has been considered but has not been found persuasive because the newly added claims are drawn to CD8+CD4 cells. Although the specification clearly supports lymphocytes being mainly CD3+, CD4-, CD8+, HLA-DR+ T cells, in the absence of the recitation of all of the cell types, the newly added claim limitations represent new matter. Further, it is noted that the term "predominantly" is not found in the specification or the claims as originally filed and there is no teaching as to any lymphocyte type that is "predominant". The subject matter claimed in claims 76-77 broadens the scope of the invention as originally disclosed in the specification.

11. Claim76-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 76-77 are indefinite in the recitation of the term "predominantly". The term is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 76-77 are indefinite in the recitation of the term CD8+CD4. The claims are indefinite because it is unclear, in the absence of an appropriate marker, whether the term is intended to mean cells with CD8+/CD4+ or CD9+/CD4-, whether somehow a new state of CD4 is being claimed. This is especially true since the specification teaches CD4+CD8+ lymphocytes at page 22, but actually claims CD4+CD8- in claims 76 and 77 in the paper submitted November 1, 1999.

Obviousness-type Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 47, 65, 66, 67, 68, 69, 70, 71, 74 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-10, of U.S. Patent No. 6,458,369.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept. The instant claims are generic to the claims of the issued patent and would have been obvious in view of the issued claims which have all of the characteristics of a method for treating a malignant tumor in a human patient comprising administering a composition comprising a therapeutically effective amount of human tumor cells that are conjugated to a hapten, are of the same tumor type as a malignant tumor of a patient for treatment of whom the composition is intended, administering said haptenized tumor cell with adjuvant, BCG, wherein said cells are autologous cells (although the cells claimed in the patent are not recited as autologous cells, since the claimed cells are claimed as "not allogeneic" autologous cells are obvious and these cells read on autologous cells because the specification of the patent teaches that non-allogeneic cells include "tumor cells produced in culture from autologous cells isolated from the patient's tumor", col 8, lines 25-27), are incapable of growing in the body of the patient, wherein the composition is administered at least six times, wherein the tumor cells are selected from the group including melanoma, lung, colon, breast, kidney, prostate tumor cells, an effective amount of cyclophosphamide, 300 mg.M.sup.2 is administered prior to administration of the composition, wherein the hapten is dinitrophenyl.

Further, although the patented claims are not drawn specifically to administration leading to elicitation of at least one of an inflammatory immune response against the tumor of said patient, a delayed-type hypersensitivity response against the tumor of said patient and activated T lymphocytes that infiltrate the tumor of said patient, given that the specification specifically teaches that "The present invention is directed to compositions containing hapten-modified tumor

cells and extracts and methods of treating cancer by administering a therapeutically effective amount of a composition containing a tumor cell or tumor cell extract to a subject in need of such treatment. The tumor cells and extracts of the invention and compositions thereof are capable of eliciting T lymphocytes that have a property of infiltrating a mammalian tumor, eliciting an inflammatory immune response to a mammalian tumor, eliciting a delayed-type hypersensitivity response to a mammalian tumor" (see abstract), the issued patent makes obvious all of the limitations of the instantly claimed invention.

14. Claims 44, 58-59, 64 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,333,028.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept. The instant claims are generic to the claims of the issued patent and would have been obvious in view of the issued claims which have all of the characteristics of a method for treating a malignant tumor, ovarian cancer, in a human patient comprising administering a composition comprising a therapeutically effective amount of autologous haptenized ovarian cancer cells, wherein the tumor cells have been treated to not grow and divide after administration to a subject and an adjuvant, wherein the hapten is DNP, wherein the adjuvant is BCG, wherein the administration elicits T lymphocytes infiltrating the ovarian cancer, elicits an inflammatory immune response against ovarian carcinoma, elicits a delay-type hypersensitivity response to the ovarian cancer cells.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 43, 44, 49-62, 64 are rejected under 35 USC 103(a) as being unpatentable over US Patent No. 5,484,596 in view of Berd et al, 1989, *Supra,* and Geczy et al, of record, *Supra.*

The claims are drawn to a composition comprising human tumor cells that are conjugated to a hapten, are of the same tumor type as a malignant tumor of a patient for whom treatment with the composition is intended, are autologous to said patient, have been rendered incapable of growing in the body of a human upon injection therein said composition eliciting an inflammatory immune response against the tumor wherein the tumor is not melanoma (claim 43), a method for

treating a malignant tumor in a human patient comprising administering said composition to the patient wherein said composition elicits, following administration of said composition with an adjuvant, at least one of an inflammatory response against the tumor, a delayed-type hypersensitivity response against the tumor and activated T lymphocytes that infiltrate the tumor (claim 44), wherein the tumor cells are selected from a group including lung, colon and kidney (claims 49, 56, 57), wherein said hapten is selected from the group including DNP and TNP (claims 50-51, 58-59), wherein the composition comprises an adjuvant, BCG (claim 52-53), the composition further comprising a carrier selected from the group consisting of saline solution and culture medium (claims 54-55), wherein the method further comprises administering a therapeutically effective amount of cyclophosphamide, 300 mg/M^2, prior to the administration of said composition (claims 60-61) further comprising sensitizing the patient to a therapeutically effective amount of 1-fluoro-2,4, dinitrobenzene prior to administering cyclophosphamide (claim 62), wherein the adjuvant is BCG (claim 64).

US Patent No. 5,484,596 claims a method of treating a malignant tumor in a human patient comprising administering autologous irradiated tumor cells in combination with adjuvant and injecting at least three doses spaced at weekly intervals (claim 1), wherein the adjuvant is BCG (claim 9). The patent specifically teaches that to prepare the vaccine for administration, the cells were centrifuged, the supernatant was removed, and 10.sup.7 viable BCG were added in a volume of 0.1 ml. Hank's Balanced Salt Solution (HBSS) was added in sufficient quantity for a final volume of 0.2 ml. US Patent No. 5,484,596 teaches that it was demonstrated in clinical studies that an objective immune response is generated on treating patients having the particular cancer by skin testing, i.e., delayed cutaneous

hypersensitivity (DCH). Immunized patients showed delayed cutaneous hypersensitivity to their own colorectal cancers" (para bridging cols 4 and 5). Further, '596 specifically teaches that treatment led to "significant improvement in both survival and disease free survival" wherein only 3 out of 20 patients had recurrence and none died, while 9 of controls had recurrence and four died (col 5, lines 12-19).

US Patent No. 5,484,596 teaches as set forth above but does not teach DNP haptenized tumor cells, does not teach administering a therapeutically effective amount of cyclophosphamide prior to administration of said composition, wherein the dose is about 300 mg/M^2, wherein the patient is sensitized with 1-fluoro-2,4-nitrobenzene prior to administration of cyclophosphamide, does not disclose that the method elicits an inflammatory immune response against the tumor.

Berd et al teach a method of successfully treating melanoma comprising administering autologous, irradiated melanoma cells to patients which caused induced delayed-type hypersensitivity and regression of metastatic tumors. Berd et al further teach a method of haptenizing said melanoma cells with DNP and specifically teach that the haptenization is an attempt to increase the efficiency of the already successful method of treatment, wherein patients are sensitized with 1-chloro -dinitrobenzene (DNCB) prior to administration of cyclophosphamide prior to administration of 300 mg/M^2 of cyclophosphamide, wherein a single administration of DNP-haptenized tumor cells results in the elicitation of delayed-type hypsersensitivity as well as a "striking" inflammatory response in tumor masses, ulceration and drainage of necrotic material with some metastases beginning to regress, infiltration of both CD4+ and CD8+ T lymphocytes into the tumor (see entire abstract).

Geczy et al specifically teach the equivalence of halogenated dinitrobenzenes such as 1-chloro and 1-fluoro-2,4-dinitrobenzene wherein each of these nitrobenzenes are conventionally used in protocols to elicit delayed hypersensitivity (p. 189,para 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of US Patent No. 5,484,596 and Berd et al and to substitute the colon cancer cells of US Patent No. 5,484,596 for the melanoma cells of Berd et al in the method of Berd et al to produce a composition comprising a DNP haptenized cancer cell and a method of treatment of cancers other than melanoma because both Berd et al and US Patent 5,484,596 specifically teach the efficacy of vaccination with autologous irradiated cancer cells and because Berd et al specifically demonstrate the increased efficacy of immune response to tumor with DNP haptenization of the tumor cells wherein, for example, T-cells infiltrate tumor. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the methods and to substitute the tumor cells of US Patent No. 5,484,596 into the method of Berd et al because US Patent No. 5,484,596 specifically teaches that their method prolongs survival and Berd et al demonstrate that their method increases efficiency of the immunization process wherein both CD4+ and CD8+ lymphocytes actually are found to infiltrate tumor, thus increased efficiency would be expected to result in increased treatment efficacy in a treatment protocol that had already been shown to be effective.

It addition, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute DNFB for the DNCB of Berd et al because the art teaches that they are equivalents, one for the other since

Geczy specifically teaches that both of these closely related halogenated dinitrobenzenes are commonly used to elicit delayed hypersensitivity. One would have a reasonable expectation of successfully substituting one of the halogenated dinitrobenzenes for the other because the art recognizes that both function to produce the same effects and are therefore functionally equivalent.

Finally, as drawn to the limitation of eliciting an inflammatory immune response against the tumor, the claimed composition appears to be the same as that of the combined references absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's product with the product of the combined prior art in order to establish that the product of the combined prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed product is functionally different than those taught by the combined prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat.App. & Int.).

Some of Applicants arguments drawn the rejection of claims 43, 44, 49-62, 64 set forth in the paper mailed November 29, 2000, Section 7, pages 5-6 are relevant to the instant rejection.

Applicant argues at page 20 of the Appeal Brief that the Braun Declaration addresses the teachings and deficiencies of the reference, Berd 1989 and states that the Berd 1989 reference lacks teachings with respect to any clinically significant tumor regression being observed as well as numbers and route of administration of the cancer cells. Applicant points to the Braun Declaration paragraphs 9 and 11. Applicant concludes that one of ordinary skill in the art would have presumed that

Berd 1989's haptenized tumor cells and BCG had been injected intra-tumorally and that the BCG was thereby responsible for the observed, clinically non-sign cant tumor responses.

A review of paragraph 9 of the declaration reveals that paragraph 9 is not drawn to clinically significant tumor regression, although it is drawn to a discussion of a definitive protocol which appears to be what Applicant is referring to when arguing "numbers and route of administration of cancer cells".

As set forth above, at paragraph 9, Dr. Braun argues that the abstract is deficient because it does not provide a definitive protocol for administration of the cells, doesn't teach how to conjugate the DNP or describe an effective protocol and in the absence of these details one of ordinary skill would be unable to practice the technology predictably. The argument has been considered but has not been found persuasive because the abstract does indeed teach a definitive protocol wherein patients with metastatic melanoma were sensitized to DNP by topical application of DNCB. Two weeks later they were injected with a vaccine consisting of 10-25 x 10(6) autologous, irradiated melanoma cells conjugated to CNP and mixed with BCG. CY 300 mg/M2 IV was given 3 days before DNCB or vaccine. Further, the abstract specifically states that "treatment of melanoma patients with autologous vaccine preceded by low dose cyclophosphamide induces delay-type hypersensitivity to melanoma cells and in some cases, regression of metastatic tumors", clearly indicating that the definitive protocol was known in the art. Given this statement, the skilled artisan would have looked to the art, in particular Berd et al (Cancer Research, 1986) *Supra*, for guidance drawn to the definitive and effective protocol. Contrary to Dr. Braun's argument, given the teachings of the

abstract and that which was known in the art, one of ordinary skill could practice the claimed invention with a reasonable expectation of success.

As set forth above, at paragraph 11 Dr. Braun argues that there is no indication that the patients described in the Berd 1989 abstract received any clinical benefit. In particular, the descriptions of inflammatory reactions, CD4 and CD8 infiltration and fluid accumulation is no indication of clinically significant tumor regression which is defined by those practiced in the art as greater than 50% reduction in tumor size without concomitant progression at other sites. Further, given the teachings of Fujiwara of the effects of sensitization with DNCB and DNP-modified tumor cells, the inflammatory reactions, CD4 and CD8 infiltration and fluid accumulation would have been expected because the patients had been sensitized to DNCB and then injected with DNP-modified tumor cells. The argument has been considered but has not been found persuasive although Dr. Braun admits on the record the known sensitization effects of DNCB and DNP-modified tumor cells, Dr. Braun is arguing limitations not recited in the claims as currently constituted as neither the specification nor the claims as originally filed is drawn to or requires "significant treatment" nor that there be 50% reduction in tumor size without concomitant progression at other sites. The claims are specifically drawn to a composition and a method for treating a malignant tumor wherein a set of defined responses to the treatment are claimed. Given that the abstract clearly teaches that tumors were beginning to regress the abstract clearly teaches that the tumors were treated.

In the interests of compact prosecution, given that both Wiseman et al and US Patent 5,484,596 specifically teach successful cancer treatment with autologous, irradiated cancer cells, it will be assumed for examination purposes

that the arguments drawn to rejections over Wiseman et al are applicable to US Patent 5,484,596.

Applicant argues that Wiseman, and by inference US Patent 5,484,596, teaches a successful alternative form of immunotherapy and Wiseman, and by inference US Patent 5,484,596, in no way suggests a deficiency or problem that would lead one of ordinary skill in the art to seek an alternative immunization strategy. The argument has been considered but has been found persuasive because Berd et al specifically teach, as set forth previously and in fact demonstrate, the increased efficiency of cancer cell vaccine with haptenization and sensitization. Thus, although Wiseman, and by inference US Patent 5,484,596, in no way suggests a deficiency or problem that would lead one of ordinary skill in the art to see an alternative immunization strategy, as set forth, it would have been prima facie obvious to modify the cells of Wiseman, and by inference US Patent 5,484,596, to increase the efficiency of the already successful treatment procedures.

Applicant argues that the Geczy reference teaches away from the claimed invention and any notion that the haptenized tumor cells could yield an anti-tumor response because they suggest an anti-hapten response and do not relate to cancer treatment, do not teach DNP haptenized tumor cells wherein the patient is sensitized with 1-fluoro-2,4-nitrobenzene prior to administration of cyclophosphamide. The argument has been considered but has not been found persuasive because the Geczy reference was cited only to provide a nexus between and demonstration of the functional identity of the DNCB successfully used by Berd et al, 1989 abstract and the claimed DNFB.

Applicant argues that even if Berd, 1989 had taught an effective immunotherapy of melanoma using haptenized, autologous melanoma cells, such a teaching would not form a sufficient basis for combination with Wiseman to achieve the claimed invention because Hoover et al, of record specifically demonstrate that although colon cancer cells are effective as a vaccine (see Hanna, of record), rectal cancer cells are not, thus, it cannot be predicted which tumor cells would be effective in haptenized vaccines for the treatment of cancer.

The argument has been considered but has not been found persuasive because although Berd et al, 1989 and the instant specification teach that autologous, irradiated melanoma cells and Hanna teaches that autologous irradiated colon cancer cells are effective for treating the respective cancers in the absence of haptenization, Hoover makes clear that there is not a similar finding for rectal cancer cells. Thus, unlike cells which have been shown to be effective vaccines, the rectal cancer cells are in fact not effective vaccines, due perhaps to a difference in the immunogenicity of the cells, or other reasons. Given that Wiseman teaches a wide variety of cancer cells that are effective for anticancer treatment and Hanna teaches colon cancer cells are effective for anticancer treatment, given that the method of Berd et al would simply be expected to increase the efficiency of the vaccine, it would be expected and could be predicted with a reasonable expectation of success that haptenization of cancer cells already demonstrated to be successful for treating cancer would also result in cancer cells that continue to be effective for treating cancer and the claims are obvious for the reasons of record.

17. Claims 47, 65-72, 74-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,484,596 in view of Berd et al, 1989,

Proceedings of the AACR, 30:382, Abstract 1515, of record, US Patent No. 5,651,993, Roitt et al (Immunology, 3rd edition, Mosby, 1993, St. Louis, pg. 2.10) and US Patent No. 5,008,183 of record, Geczy et al, of record.

The claims are drawn to a method of treating a malignant tumor in a patient comprising administering to the patient a composition comprising a therapeutically effective amount of tumor cells that are conjugated to a hapten, adjuvant, are of the same tumor type as a malignant tumor of the patient, are autologous to said patient and have been rendered incapable of growing in the body of a human upon injection therein, said composition eliciting at least one of the following upon administration to said patient with an adjuvant: an inflammatory immune response against the tumor; a delayed-type hypersensitivity response against the tumor; and activated T lymphocytes that infiltrate the tumor and repeating said administration at least six times at spaced apart intervals (claim 47), wherein said tumor cells/cancer are selected from the group consisting of melanoma cancer, lung cancer, colon cancer, breast cancer, kidney cancer, prostate cancer (claim 65-66) wherein said hapten is selected from the group including DNP (claims 67-68), wherein the method further comprises administering a therapeutically effective amount of cyclophosphamide prior to administration of said composition, wherein the dose is about 300 mg/M^2 (claims 69-71), wherein the patient is sensitized with 1-fluoro-2,4-nitrobenzene prior to administration of cyclophosphamide (claim 72) wherein the adjuvant is BCG (claim 74), wherein the life of the patient is prolonged (claim 75).

US Patent No. 5,484,596 claims a method of treating a malignant tumor in a human patient comprising administering autologous irradiated tumor cells in combination with adjuvant and injecting at least three doses spaced at weekly

intervals (claim 1), wherein the adjuvant is BCG (claim 9). US Patent No. 5,484,596 teaches that it was demonstrated in clinical studies that an objective immune response is generated on treating patients having the particular cancer by skin testing, i.e., delayed cutaneous hypersensitivity (DCH). Immunized patients showed delayed cutaneous hypersensitivity to their own colorectal cancers" (para bridging cols 4 and 5). Further, '596 specifically teaches that treatment led to "significant improvement in both survival and disease free survival" wherein only 3 out of 20 patients had recurrence and none died, while 9 of controls had recurrence and four died col 5, lines 12-19.

US Patent No. 5,484,596 teaches as set forth above but does not teach DNP haptenized tumor cells, does not teach administering a therapeutically effective amount of cyclophosphamide prior to administration of said composition, wherein the dose is about 300 mg/M^2, wherein the patient is sensitized with 1-fluoro-2,4-nitrobenzene prior to administration of cyclophosphamide, administration of composition at least six times.

Berd et al teach a method of successfully treating melanoma comprising administering autologous, irradiated melanoma cells to patients which caused induced delayed-type hypsersensitivity and regression of metastatic tumors. Berd et al further teach a method of haptenizing said melanoma cells with DNP and specifically teach that the haptenization is an attempt to increase the efficiency of the already successful method of treatment, wherein patients are sensitized with 1-fluoro-2,4-nitrobenzene prior to administration of cyclophosphamide prior to administration of 300 mg/M^2 of cyclophosphamide, wherein a single administration of DNP-haptenized tumor cells results in the elicitation of delayed-type hypsersensitivity as well as a "striking" inflammatory response in tumor

masses, ulceration and drainage of necrotic material with some metastases beginning to regress, infiltration of both CD4+ and CD8+ T lymphocytes into the tumor (see entire abstract).

US Patent No. 5,651,993 specifically teaches that conventional vaccination relies upon inoculation of a patient with an antigen to establish a primary immune response. Two basic types of cells are generated during a primary immune response: effector cells for cell-mediated immunity and memory cells. Each of these cell types originates from lymphocytes that are reactive with the antigen used for the primary immunization. Subsequent exposure to antigen quickly boosts the level of memory cells, thereby producing high levels of antibodies specific for antigen (para 53 of the Detailed Description Text).

Roitt et al specifically teach that upon generation of memory cells, the memory cells recirculate and home to T- or B-dependent areas of lymphoid tissues where they stay, ready to respond if the same antigen is encountered again (p. 2.10, col 2).

US Patent No. 5,008,183 specifically teaches conventional methods of immunization to produce immune cells wherein it is recognized that optimal antibody titers may vary, wherein boosting is used to increase titers of antibodies and the titer of antibody is checked/assayed with conventional methods, until the desired titers are obtained (col 3-4), wherein the patent teaches an identified range of readministrations ranging from 2-6 for achieving antibody titers in the optimal range (col 5, lines 50-54) and finally teaches that the need for boosters can be determined by monitoring blood levels (col 7, lines 33-44).

Geczy et al specifically teach the equivalence of halogenated dinitrobenzenes such as 1-chloro and 1-fluoro-2,4-dinitrobenzene wherein each of

these nitrobenzenes are conventionally used in protocols to elicit delayed hypersensitivity (p. 189,para 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of US Patent No. 5,484,596 and Berd et al and to substitute the colon cancer cells of US Patent No. 5,484,596 for the melanoma cells of Berd et al in the method of Berd et al to produce a composition comprising a DNP haptenized colon cancer cell and a method of treatment for the treatment of colon cancer because both Berd et al and US Patent 5,484,596 specifically teach the efficacy of vaccination with autologous irradiated cancer cells and because Berd et al specifically demonstrates and suggests the increased efficacy of immune response to tumor with DNP haptenization of the tumor cells wherein, for example, T-cells infiltrate tumor. One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the tumor cells of US Patent No. 5,484,596 into the method of Berd et al because US Patent No. 5,484,596 specifically teaches that their method prolongs survival and Berd et al demonstrate that their method increases efficiency of the immunization process wherein both CD4+ and CD8+ lymphocytes actually are found to infiltrate tumor, thus increased efficiency would be expected to result in increased treatment efficacy.

Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to repeat administration at least six times at spaced apart intervals because the art recognizes, as taught by US Patent No. 5,651,993, that conventional vaccination relies upon inoculation of a patient with an antigen to establish a primary immune response and that two basic types of cells are generated thereby, not only effector cells but also memory cells and that

subsequent exposure to antigen quickly boosts the level of memory cells, producing high levels of antibodies specific for antigen. Further the art recognizes as taught by Roitt et al that not only B- memory cells are produced but also T-memory cells are produced and thus it would be expected that upon boosting, that is re-exposing the memory cells to the antigen (in this case cancer cells) that not only high levels of antibodies but also high levels of effector T-cells would be produced.

Further, although not drawn specifically to determining the optimum repeated administrations for effective treatment, but rather to optimum administrations for a particular level of antibody titer, the teachings of US Patent No. 5,008,183 are clearly relevant to the instant rejection. In particular, US Patent No. 5,008,183 specifically teaches the general principles of producing and boosting an immune response by administering and readministering antigen, teaches conventional methods of determining efficacy of immune response, teaches not only ranges of boosting for optimization also methods of identifying ranges of administrations that will produce the desired immune response and methods for determining the need for boosters.

Given that one of ordinary skill in the art would have had a reasonable expectation of successfully treating a malignant colon tumor in a human by administering three doses of the haptenized colon cancer cell of the combined references because only three doses of non-haptenized vaccine at spaced apart intervals led to significant improvement in both survival and disease free survival, given that boosting and optimization of immune responses was well known in the art, given the normal desire of scientists or artisans to improve upon what is generally already known, given that discovery of an optimum value of a result

effective variable in a known process is ordinary within the skill of the art, given that conventional boosting protocols and ranges were known in the art, given that no unexpected result for the method of treatment with at least six repeated administrations has been disclosed, it would have been *prima facie* obvious to, and one of ordinary skill in the art would have been motivated to practice the method with different number of boosting administrations, including at least six repeated administrations in order to determine the number of boosts that would result in the optimum outcome for patients.

Finally, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute DNFB for the DNCB of Berd et al because the art teaches that they are equivalents, one for the other since Geczy specifically teaches that both of these closely related halogenated dinitrobenzenes are commonly used to elicit delayed hypersensitivity. One would have a reasonable expectation of successfully substituting one of the halogenated dinitrobenzenes for the other because the art recognizes that both function to produce the same effects and are therefore functionally equivalent.

In the interests of compact prosecution, given that both Wiseman et al and US Patent 5,484,596 specifically teach successful cancer treatment with autologous, irradiated cancer cells, it will be assumed for examination purposes that the arguments drawn to rejections over Wiseman et al are applicable to US Patent 5,484,596.

Some of Applicant's arguments drawn to the rejection of claims 47, 65-72, 74-75 set forth in the paper mailed November 29, 2000, Section 5, pages 3-4 are relevant to the instant rejection.

As drawn to the Berd, 1989 abstract, Applicant at page 12 of the Appeal Brief states that the Berd 1989 abstract has been discussed above and in the Braun Declaration) noting the lack of guidance and expectation of success of this reference. A review of page 10 of the Brief reveals the argument that the Berd 1989 abstract fails to provide a definite protocol that would permit one to repeat the work, determine whether this approach elicited an immune response to unmodified cells or establish that it achieved any clinical benefit and points specifically to the Braun declaration at paragraphs 7, 9, 10, 11.

A review of the Braun declaration paragraphs 7, 9, 10, 11 reveals that Dr. Braun argues at paragraph 7 that the abstract presents preliminary observations from a new protocol and states that the abstract itself states that the findings are preliminary. Dr. Baun further argues that nothing in the abstract suggests that this approach addresses the fundamental questions of tumor vaccination raised in a review article coauthored by Dr. Braun including questions raised as to which type of immune response is most important to a host response, whether whole cells or extracts should be used, whether to use adjuvants or cytokines, whether an antitumor response would lead to autoimmunity, whether to use autologous or syngeneic cells. Further the haptenization protocol raises a new issue.

Dr. Braun's arguments have been considered but have not been found persuasive because whether or not the abstract addresses fundamental questions of tumor vaccination is not relevant because the abstract makes quite clear that the haptenization method is being used to increase the efficiency of a protocol that had been previously used to successfully treat melanoma, that is, the abstract specifically states that "treatment of melanoma patients with autologous vaccine precede by low dose cyclophosphamide induces delay-type hypersensitivity to

melanoma cells and in some cases, regression of metastatic tumors". Further, it is clear, given that the abstract specifically teaches that administration of only a single dose of the vaccine resulted not only in erythema and ulceration followed by drainage of necrotic material and some regression of tumor, but also resulted in softening of tumor, that is changing from rock hard to fluctuant consistency that these results are consistent with and recognized by those of ordinary skill to be evidence of clinical regression. In particular, those of skill in the art and Dr. Berd in particular understand that erythema, softening and diminution in size of tumor are all evidence of clinical regression (see Murphy et al, Lab Invest., 1990, 62(1),70A, of record), that is treatment of a tumor. Although the abstract states that the results are preliminary, given that the melanoma cells, even in the absence of hapten successfully treated melanoma, given that even with only a single dose of haptenized melanoma cell vaccine, the vaccine successfully led to clinical regression in 70% of the patients treated presented with clinical regression, one would have a reasonable expectation of successfully treating melanoma with the construct and method of Berd, 1989.

In paragraph 9, Dr. Braun argues that the abstract is deficient because it does not provide a definitive protocol for administration of the cells, doesn't teach how to conjugate the DNP or describe an effective protocol and in the absence of these details one of ordinary skill would be unable to practice the technology predictably. The argument has been considered but has not been found persuasive because the abstract does indeed teach a definitive protocol wherein patients with metastatic melanoma were sensitized to DNP by topical application of DNCB. Two weeks later they were injected with a vaccine consisting of 10-25 x 10(6) autologous, irradiated melanoma cells conjugated to CNP and mixed with BCG.

CY 300 mg/M2 IV was given 3 days before DNCB or vaccine. Further, abstract specifically states that "treatment of melanoma patients with autologous vaccine preceded by low dose cyclophosphamide induces delay-type hypersensitivity to melanoma cells and in some cases, regression of metastatic tumors". Clearly indicating that the definitive protocol was known in the art. Given this statement, the skilled artisan would have looked to the art, in particular Berd et al (Cancer Research, 1986,), *Supra* for guidance drawn to the definitive and effective protocol. Further, Examiner takes note that methods of conjugation of the cells to DNP for immunological protocols was well known in the art at the time the invention was made, see for example, von Blomberg et al (Immunology, 1980, 39:291-299) attached hereto. Contrary to Dr. Braun's argument, given the teachings of the abstract and that which was known in the art, one of ordinary skill could practice the claimed invention with a reasonable expectation of success.

At paragraph 10, Dr. Braun argues that there is no indication in the protocol that patients have developed an immune response to unmodified cells and that the abstract does not teach that non-haptenized tumor cells induced DTH to melanoma cells. The argument has been considered but has not been found persuasive because the finding described in the abstract is not surprising given the art recognition that haptens are useful to sensitize hosts against haptenized target cells, see Applicant's arguments drawn to Fugiwara above.

Applicant further argues, that the vaccine protocol of the invention comprising injection of hapten-modified autologous tumor cells resulted in DTH to autologous non-haptenized tumors cells is an event that could not have been anticipated nor expected as a result of what is described in the Berd 1989 abstract or from what was known in the literature. The argument is moot as drawn to the

previous rejection because the instant rejection does not rely on Murphy et al. However, in the interests of compact prosecution, it is noted that US Patent No. 5,484,596 specifically teaches that "Immunized patients showed delayed cutaneous hypersensitivity to their own colorectal cancers." in the absence of hapten conjugation. Given this teaching, it would be neither surprising nor unexpected that patients who had been administered haptenized cell vaccine, wherein haptens are known to be useful for sensitizing hosts, would present with DTH to the unmodified tumor cells and the claims are obvious for the reasons set forth above.

At paragraph 11 Dr. Braun argues that there is no indication that the patients described in the Berd 1989 abstract received any clinical benefit. In particular, the descriptions of inflammatory reactions, DD4 and CD8 infiltration and fluid accumulation is no indication of clinically significant tumor regression which is defined by those practiced in the art as greater than 50% reduction in tumor size without concomitant progression at other sites. Further, given the teachings of Fujiwara of the effects of sensitization with DNCB and DNP-modified tumor cells, the inflammatory reactions, DD4 and CD8 infiltration and fluid accumulation would have been expected because the patients had been sensitized to DNCB and then injected with DNP-modified tumor cells.

The argument has been considered but once again has not been found persuasive because although Dr. Braun presents a definition of clinical benefit, as set forth above, those of skill in the art and Dr. Berd in particular understand that erythema, softening and diminution in size of tumor are all evidence of clinical regression. Further, although this argument is moot as drawn to the previous rejection because the instant rejection does not rely on Murphy et al, in the interests of compact prosecution it is noted that given that the colon cancer cells of

US Patent No. 5,484,596, even in the absence of hapten successfully treated colon cancer, given that Berd et al teach that even with only a single dose of haptenized melanoma cell vaccine, the vaccine successfully led to clinical regression in 75% of the evaluable patients treated, wherein Berd et al specifically demonstrate the increased efficacy of immune response to tumor with DNP haptenization of the tumor cells wherein, for example, T-cells infiltrate tumor, it is clear that the haptenization protocol led to increased efficiency of a successful protocol and contrary to Dr. Braun's argument one would have had a reasonable expectation of success of using the protocol of the combined references to treat, for example, colon cancer.

The arguments in the Braun declaration, as they are drawn to the supposed inadequacies of the Berd, 1989 abstract have been carefully considered but have not been found persuasive for the reasons set forth above.

Applicant argues at page 10 of the Brief that since the Berd 1989 reference fails to provide any expectation of success this reference is irrelevant for providing any expectation of success for such an approach to other types of cancer and no other reference cited by Examiner makes up for this fundamental flaw. The argument has been considered but for the reasons set forth above, the Berd, 1989 abstract provides a reasonable expectation of success when combined with other references for the reasons set forth above.

As drawn to the Geczy reference, Applicant argues at page 13 of the Brief that Geczy does not pertain to cancer therapy and that Geczy's anti-hapten responses would not be useful for tumor treatment since they would attack the haptenized tumor cell vaccine itself instead of residual tumor cells. The argument has been considered but has not been found persuasive because the Geczy

reference was cited only to provide a nexus between and demonstration of the functional identity of the DNCB successfully used by Berd et al, 1989 abstract and the claimed DNFB. Further, although Applicant states that Geczy's anti-hapten responses would not be useful for tumor treatment, it is noted that Dr. Braun in the Declaration discussed above specifically argues that those of skill in the art would expect the reported positive reactions on the tumors, given the teaching of Fujiwara, Sherman and others drawn to known effects of using haptens to sensitize hosts against haptenized target cells.

18. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date of February 28, 1994 for claims 47, 65-72, 74-77 of the instantly claimed application serial number 08/203,004, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

19. No claims allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at 571-272-0898. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
May 4, 2007